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STATE INSTITUTE FOR DRUG CONTROL
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Public Assessment Report

Scientific discussion

Apremilast Krka d.d.
Apremilast Krka
Apremilast HCS

apremilast

SK/H/0306/001-002/DC
SK/H/0307/001-002/DC
SK/H/0309/001-002/DC

Date: 09/2024

This module reflects the scientific discussion for the approval of Apremilast Krka. The procedure was finalised at 28 April 2024. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Apremilast Krka d.d. and Apremilast Krka, 10 mg+20 mg+30 mg film coated tablets (initiation pack) and 30 mg film coated tablets, from KRKA tovarna zdravil d.d. Novo mesto and Apremilast HCS10 mg+20 mg+30 mg film coated tablets (initiation pack) and 30 mg film coated tablets form HCS BV.
(for the purposes of this report name Apremilast Krka is used)

The product is indicated for*:*

Psoriatic arthritis
<Invented name>, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy (see section 5.1).

Psoriasis
<Invented name> is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

Behçet's disease
<Invented name> is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

A comprehensive description of the indications and posology is given in the SmPC."

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Apremilast Krka are film-coated tablets (tablets).
10 mg film-coated tablets are pink, round, biconvex, film-coated tablets marked with 10 on one side of the tablet. Tablet dimension: diameter approx. 6 mm.
20 mg film-coated tablets are orange, brown, round, biconvex, film-coated tablets marked with 20 on one side of the tablet. Tablet dimension: diameter approx. 8 mm.
30 mg film-coated tablets are light brownish violet, round, biconvex, film-coated tablets marked with 30 on one side of the tablet. Tablet dimension: diameter approx. 10 mm.

Apremilast Krka d.d./ Apremilast Krka/Apremilast HCS is available as

Treatment initiation pack, in OPA/Alu/PVC//Alu blisters.
Each initiation pack of 27 film-coated tablets contains 4 film-coated tablets of apremilast

10 mg, 4 film-coated tablets of apremilast 20 mg and 19 film-coated tablets of apremilast 30 mg

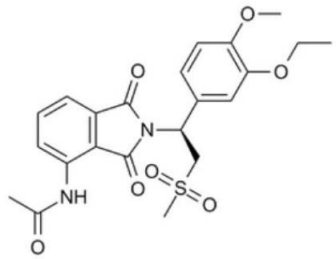
and

Apremilast Krka d.d. 30 mg film-coated tablets in OPA/Alu/PVC//Alu blisters containing 56 film-coated tablets.
Apremilast Krka 30 mg/ Apremilast HCS 30 mg in OPA/Alu/PVC//Alu blisters containing 14, 56 or 168 film-coated tablets.

II.2 2.2Drug Substance

The drug substance is apremilast.

Structural formula:



Molecular Formula: $C_{22}H_{24}N_2O_7S$

Appearance: white to yellow white powder

Solubility: slightly soluble in methanol, soluble in acetone, freely soluble in dichloromethane, practically insoluble in water and HCl, and very slightly soluble in NaOH

Stereochemistry and isomerism: Apremilast has one chiral centre therefore two isomers are possible.

Polymorphism: Apremilast is known to exist in several polymorphic forms (anhydrous, solvate or amorphous form).

Manufacturing: This drug substance is not described in the European Pharmacopoeia. For the quality documentation of the drug substance, the applicant refers to the ASMF from the API manufacturer. Detailed information on the manufacturing of the active substance has been provided in the ASMF and it was considered satisfactory.

II.3 Medicinal Product

Pharmaceutical development:
The finished product was developed as a generic to Otezla 10 mg, 20 mg and 30 mg film-coated tablets marketed by Amgen Europe BV and it is manufactured in all three strengths 10 mg, 20 mg and 30 mg by Krka, d.d., Novo mesto, Slovenia. The development of the product is described in sufficient detail. The highest strength of drug product (strength 30 mg) was included in the BE study. *In vitro* dissolution comparisons in support of biowaiver of 10 mg

and 20 mg strengths were performed.

Manufacture of the product:
Manufacturing process is a standard process consists of the following steps: blending (compression mixture), tableting, film coating and packaging. Manufacturing flow chart was provided. Description of manufacturing process is provided in sufficient detail.

Product specification:
The proposed specification for the finished product is in line with ICH Q6A and Ph. Eur. 0478 for Tablets, where relevant, and is generally acceptable. Risk assessment for elemental impurities and Risk evaluation for nitrosamine impurities have been provided.

Stability of the product:
Stability data were provided for three batches of each strength under long-term and accelerated conditions which were packed in OPA/Al/PVC-Al blister as proposed for marketing. The proposed shelf life of 24 months is considered acceptable. Proposed storage condition "This medicinal product does not require any special storage condition" is acceptable as it is in line with stability data and CPMP/QWP/609/96/Rev 2 requirements.

II.4 Discussion on chemical, pharmaceutical and biological aspects

From a quality point of view the dossier was adequately presented

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of apremilast are well known. As apremilast is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. Overview was based on literature review which was considered appropriate.

The non-clinical sections of the SmPC are in line with the reference product Otezla.

A new excipient, mannitol, is included in the formulation of apremilast, while lactose is excluded in comparison with reference medicinal product. If mannitol is used orally in excessive doses, laxative symptoms may occur; however, the amount of a maximal daily dose of mannitol does not exceed the action limit of 10 g for warning of laxative effects.

No impurities are individually specified in apremilast film-coated tablets.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Apremilast Krka is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

As apremilast is a widely used, well-known active substance, the applicant has not provided additional studies and further non-clinical studies were not required. This approach is acceptable for generic applications.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the application, the applicant has submitted as report one bioequivalence study conducted under fasting conditions as a randomized, single-dose, crossover, 2-treatment, 2-period, 2-sequence, comparative bioavailability study of Apremilast 30 mg film-coated tablets and Otezla® 30 mg film-coated tablets in healthy male and female subjects and

Dissolution profiles of apremilast were performed with test (Apremilast 30 mg film-coated tablets) and reference (Otezla® 30 mg film-coated tablets) formulations applied in bioequivalence study.

For 10 mg and 20 mg strength proportionality based biowaiver was submitted.

The strengths of Apremilast 10, 20 and 30 mg are proportional from the quantitative and qualitative perspective. The in vitro dissolution profiles are comparable between the various strengths. Various strengths are manufactured by the same manufacturing process.

Table 1. Pharmacokinetic parameters

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test Product	Reference Product
$AUC_{(0-T)}$ (ng·h/mL)	2686.64 (±993.02)	2792.16 (±972.78)
$AUC_{(0-\infty)}$ (ng·h/mL)	2783.81 (±1101.17)	2874.11 (±1065.42)
C_{max} (ng/mL)	296.51 (±80.64)	317.80 (±80.03)
T_{max}[1] (hours)	3.00 (1.00 – 5.00)	3.50 (0.63 – 5.00)

[1] Median (Min, Max)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	Confidence Intervals (%)	CV%[1]
$AUC_{(0-T)}$	95.53	92.23 – 98.94	9.8
C_{max}	92.89	88.45 – 97.56	13.7

[1] Estimated from the Residual Mean Squares

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Apremilast Krka is considered bioequivalent with Otezla.

The results of study with 30 mg formulation can be extrapolated to other strengths 10 mg and 20 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.2 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Apremilast Krka.

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	Serious events of hypersensitivity
	Suicidality
	Serious events of depression
Important potential risks	Vasculitis
	Malignancies
	Serious events of anxiety and nervousness
	Serious infections and transmission including opportunistic infections and transmission of infections through live vaccines
	Major adverse cardiac (MACE) and tachyarrhythmia
	Prenatal embryo-fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast
Missing information	Long-term safety

IV.3 Discussion on the clinical aspects

Submitted clinical dossier was of sufficient quality. Submitted data supported the chosen legal basis “generic application”. Bioequivalence between the test product Apremilast Krka with the reference medicinal product Otezla has been demonstrated based on provided data.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed based on a bridging report making reference to reference medicinal product Otezla; EMEA/H/C/003746 for content (key safety messages) and Desloratadine 5 mg film-coated tablets; EMEA/H/C/002310 for layout /design/format. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

These were the applications for a marketing authorisation of a medicinal product for human use as it is defined in Article 10(1) (generic application) of the European Directive 2001/83/EC as amended.
Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovak Republic acting as RMS.
The Applicant Krka d.d. Novo Mesto, Slovenia, has submitted duplicate MAAs under procedural numbers SK/H/0306,0307, 0309/001-002/DC.

CMS were:
SK/H/0306/001-002/DC: CMSs are Czechia, Estonia, Hungary, Lithuania, Latvia, Poland, Slovenia
SK/H/0307/001-002/DC: CMSs are Germany, Spain, Finland, Ireland, Italy, Sweden
SK/H/0309/001-002/DC: CMSs are Austria, Belgium, Germany, France, the Netherlands

As the reference medicinal product Otezla (MAA No: EU/1/14/981/001-003, MAH: Amgen Europe BV, the Netherlands) was chosen.

Quality aspects of the dossier were adequately described; specifications of apremilast were adequately drawn up and that of finished medicinal product were in line with ICH Q6A.

As apremilast is a widely used, well-known active substance, the applicant has not provided additional studies, and further non-clinical studies were not required.

To support the applications, the applicant has submitted as report one bioequivalence study conducted under fasting conditions as a randomized, single-dose, crossover, 2-treatment, 2-period, 2-sequence, comparative bioavailability study of Apremilast 30 mg film-coated tablets and Otezla® 30 mg film-coated tablets in healthy male and female subjects and

Dissolution profiles of apremilast were performed with test (Apremilast 30 mg film-coated tablets) and reference (Otezla® 30 mg film-coated tablets) formulations applied in submitted bioequivalence study.
For 10 mg and 20 mg strength proportionality based biowaiver was submitted.

Bioequivalence between the test product Apremilast Krka with the reference medicinal product Otezla has been demonstrated based on provided data.